Cardiovascular Management in Pregnancy
Antithrombotic Agents and Antiplatelet Agents

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Thrombotic complications of pregnancy are a major cause of morbidity and mortality to the mother and fetus. Pulmonary embolism is a leading cause of maternal death and accounts for 10.3% of all maternal deaths in the United States.[1,2] Overall, pregnancy increases the risk of venous thromboembolism (VTE) 5-fold, with an additional increase in risk in the postpartum period.[3,4]

Pregnancy is associated with a hypercoaguable state attributable to relative increases in fibrinogen, plasminogen activator inhibitors, clotting factors VII, VIII, and X, von Willebrand Factor, and platelet adhesion molecules, and relative decreases in protein S activity, as well.[5,6] Pregnancy is also a time of dramatic hemodynamic change including a reduction in lower extremity venous flow velocity by up to 50% at the end of the second trimester, which persists until 6 weeks postpartum.[7]

Recommendations for thrombosis prevention and anticoagulation in pregnant women are derived largely from algorithms from the nonpregnant population. We review the use of both older and new anticoagulants and antiplatelet medications during pregnancy and highlight their clinical utility in conditions including VTE, thrombophilias, mechanical heart valves, antiphospholipid syndrome (APLS), preeclampsia, intrauterine growth restriction (IUGR), and placental abruption.

Medications: Anticoagulants

Vitamin K Antagonists

Warfarin

Warfarin is a vitamin K antagonist that easily crosses the placenta.[8] Exposure in the first trimester is associated with warfarin embryopathy characterized by nasal bone hypoplasia and stippled epiphyses.[9] Case series of pregnant women taking warfarin in the setting of mechanical heart valves found warfarin embryopathy rates of 5.6% and 6.4%, respectively.[10,11] Warfarin use in the second and third trimester is associated with possible neurological sequelae including seizures, developmental delay, and hypotonia in the developing fetus attributable to intracranial microhemorrhages.[12] Increased fetal risk for hemorrhage has been attributed to the greater affinity of albumin for bilirubin than warfarin, high serum bilirubin concentration, reduced hepatic drug metabolism, and poor synthesis of vitamin K–dependent factors.[10] Because of this embryopathy, warfarin is Food and Drug Administration category X (Table 1). However, the recent American Heart Association/American College of Cardiology (AHA/ACC) Valvular Heart Disease Guidelines recommend warfarin in pregnant patients with a mechanical prosthesis to achieve a therapeutic international normalized ratio (INR) in the second and third trimesters with discontinuation of warfarin with the initiation of intravenous unfractionated heparin (UFH) before a planned delivery.[13]

Dose-Dependent Effects

The fetal impact of warfarin appears to be dose dependent. Cotrufo et al[10] found that a warfarin dose >5 mg daily was significantly associated with poor pregnancy outcome, including miscarriage, stillbirth, or embryopathy. These investigators have documented a 15% risk of pregnancy complications in women receiving warfarin daily doses of ≤5 mg in comparison with an 88% risk in women receiving higher doses.[14] This dose-dependent risk was replicated by Khamooshi et al.[15] In a retrospective study of 196 pregnancies over 3 decades, they compared fetal and maternal complications among women with mechanical heart valves who used warfarin throughout pregnancy with women who substituted subcutaneous heparin during the first 12 weeks and last 2 weeks of pregnancy and found that women who achieved INR of 2.5 to 3.5 with ≤5 mg of warfarin daily had better maternal outcomes and less fetal loss than the heparin group. Continuation of warfarin during the first trimester is reasonable for pregnant women with a mechanical valve if the dose of warfarin to achieve a therapeutic INR is ≤5 mg (AHA/ACC Guidelines Class IIA recommendation).[13]

In a small study evaluating a lower target INR range (1.5–2.5) in pregnant women with newer-generation mechanical aortic valves, there were no reported maternal thrombotic events or neonatal complications in 16 pregnancies in which warfarin dosing was maintained at <5 mg daily.[16] Although this study is promising, more data are needed before recommendations to lower the target INR for pregnant women with mechanical heart valves can be made.

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Warfarin is safe for breastfeeding women and is recommended by the American College of Obstetrics and Gynecology as the first-line anticoagulant for the immediate postpartum period for all indications. Two small but seminal studies demonstrate neither detectable warfarin level nor change in prothrombin time of the infant breastfed by a mother on therapeutic doses.[17,18]

Heparin-Based Anticoagulants

Unfractionated Heparin

UFH is a mix of large polar molecules that interact with factors X and II. It has been used in pregnancy both for treatment and prevention of thromboembolism and for obstetric indications such as recurrent pregnancy loss, prevention of preeclampsia, and prevention of IUGR.

The large molecular size of UFH prevents it from crossing the placenta and from passing into breast milk.[19] Certain high-dose UFH formulations include benzyl alcohol as a bacteriostatic preservative. Administration of medications with benzyl alcohol directly to the neonate is associated with a neurological syndrome associated with characteristic gasping at birth.[20] Therefore, our practice is to use only preservative-free heparin formulations for pregnant women.[21]

A 2010 Cochrane review of the use of heparins, including UFH and low-molecular-weight heparin (LMWH), for VTE prophylaxis found a slightly increased incidence of antenatal bleeding events among anticoagulated women in comparison with placebo.[22] There was also a nonsignificant trend toward increased postpartum bleeding after cesarean delivery. The short half-life of UFH and ease of reversibility is particularly suited to third trimester usage. The ability to correct partial thromboplastin time within 4 hours of the last dose decreases the rate of postpartum bleeding and allows the safe use of regional anesthesia. Heparin-induced thrombocytopenia is substantially more rare in pregnant patients than the nonpregnant population.[23]

Osteoporosis, a well-described risk of prolonged UFH use outside of pregnancy, has an estimated incidence during pregnancy of 2% to 5%.[24–26] This association appears to be substantially stronger with UFH than with LMWH.[27] The challenge in identifying new bone loss in the setting of a medication during pregnancy is the nearly ubiquitous lack of prepregnancy data; however, the lack of data does not eliminate the possibility of impact. At this point, there is no evidence to guide mitigation of this potential side effect such as prophylaxis with vitamin D or calcium supplementation. In the rare event of fracture in a woman on LMWH, medication effect must be included in the differential diagnosis.[28]

In the first and second trimester, increases in heparin-binding proteins, glomerular filtration rate, coagulation factors, and volume of distribution affect the dose required to attain prophylactic or therapeutic levels. As the placenta matures, it degrades heparin, leading to increased dosages across trimesters.[29,30] In the third trimester, increased levels of fibrinogen and factor VII create an environment of relative heparin resistance.[31] Therefore, monitoring of activated partial thromboplastin time levels throughout pregnancy is necessary to ensure target levels in women who are anticoagulated.

There are no large trials that offer evidence-based prophylactic dosing of UFH in pregnancy. Based on pharmacokinetics and American College of Obstetricians and Gynecologists and American College of Chest Physicians recommendations, we follow trimester-specific dose parameters[32] (Table 2). The postpartum period is classically considered the 6 weeks following delivery. Recent data have suggested that increased thrombogenicity persists for 12 weeks after delivery; however, at this time there are no recommendations to extend anticoagulation for the additional 6 weeks.[33]

Low-Molecular-Weight Heparin

LMWHs offer advantages over UFH, including a longer half-life, efficacy with once daily dosing, and weight-based dosing.[34] There are no documented fetal or neonatal risks to maternal use of LMWH during pregnancy. Multiple studies confirm that LMWH does not cross the placenta and therefore does not confer human teratogenic risk. In addition, there are no reports of neonatal bleeding among offspring of mothers treated with LMWH, and coagulation profiles from cord samples do not show any abnormalities.[35]

Dosing of LMWH should be adjusted in pregnancy. Prophylactic dosing is daily, similar to the nonpregnant population. However, increased renal clearance can theoretically truncate levels toward the end of the 24-hour period. The LIVE-ENOX trial demonstrated that both 40 mg and 80 mg daily were safe prophylactic doses in pregnancy relative to maternal or neonatal bleeding.[36] Given their equivalent efficacy and safety, the lower dose may be more cost-effective, but this has not been studied systematically. Neither the American College of Obstetrics and Gynecology nor

Table 1. FDA Pregnancy Categories

Category	Evidence
A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters.)
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.
C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
X	Studies in animals or humans have demonstrated fetal abnormalities and there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

FDA indicates Food and Drug Administration.

Table 2. Recommended Dosing of Anticoagulants (From ACOG Practice Bulletin 123)

Medication	Timing	Dosage
Prophylactic LMWH	Throughout pregnancy	Enoxaparin 40 mg SC daily
		Dalteparin 5000 U SC daily
		Tinzaparin 4500 U SC daily
Therapeutic LMWH	Throughout pregnancy	Enoxaparin 1 mg/kg every12 h
		Dalteparin 200 U/kg daily
		Dalteparin 100 U/kg every 12 h
		Tinzaparin 100 U/kg every 12 h
Minidose prophylactic UFH	Throughout pregnancy	UFH 5000 U SC every 12 h
Prophylactic UFH	Throughout pregnancy	UFH 5000–10 000 U SC every 12 h
	First trimester	UFH 5000–7500 U SC every 12 h
	Second trimester	UFH 7500–10 000 U SC every 12 h
	Third trimester	UFH 10 000 U SC every 12 h, unless aPTT elevated
Therapeutic UFH	Throughout pregnancy – adjust to target aPTT	≥10 000 U SC every 12 h
Postpartum anticoagulation	Through 6 wk after delivery	Prophylactic LMWH/UFH 5000 U SC every 12 h
		LMWH/UFH bridge to warfarin with target INR of 2.0–3.0

aPTT indicates activated partial thromboplastin time; INR, international normalized ratio; LMWH, low-molecular-weight heparin; SC, subcutaneously; and UFH, unfractionated heparin.

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the American College of Chest Physicians recommend following anti-Xa levels for LMWH used for thrombosis prophylaxis.

Both the American College of Obstetricians and Gynecologists and the American College of Chest Physicians recommend twice daily dosing for prophylactic LMWH. One small study demonstrated that in pregnancy, 1.5 mg/kg SC once daily is equivalent to 1 mg/kg SC enoxaparin every 12 hours. Although this study is limited by a small sample size it may offer a helpful alternative for the patient who cannot comply with 2 injections per day.[37]

In contrast to prophylactic dosing, therapeutic dosing of LMWH is weight based. The more common LMWHs available in the United States, enoxaparin and dalteparin, are administered every 12 hours. Gestational weight gain must be considered when calculating doses and adjustment may still be necessary to attain appropriate anti-Xa levels. Barbour et al[38] studied 13 pregnancies requiring therapeutic anticoagulation with dalteparin. They followed peak anti-Xa activity in all patients and found that 85% required uptitration of their dose beyond the weight-based recommendations.

There are increasing data that pregnant women with mechanical heart valves on LMWH might be better monitored by following trough levels as well. Goland et al[39] studied 30 pregnant women and found subtherapeutic (<6 U/L) levels at trough points among all women who had peak levels checked. Even among women with supratherapeutic peak levels, 31% had subtherapeutic troughs. Furthermore, Berresheim et al[40] recently published a case series of 4 pregnant women with mechanical heart valves and compared the management of LMWH with pregnant women with VTE. They noted that, despite both uptitration beyond weight-based dosing and achievement of adequate anti-Xa levels, none of their subjects had adequate trough levels. As with UFH, there are no large trials to direct optimal dosing. At our institution, we routinely monitor peak anti-Xa levels in our pregnant women requiring therapeutic LMWH with a target level of 0.8 to 1.2 U/mL 4 to 6 hours after dosing depending on the indication, but we will consider addition of trough levels for future patients based on new data.

Several studies have examined the safety of enoxaparin in pregnancy.[41–43] The details are highlighted in Table 3.

Table 3. Studies Evaluating Safety of Enoxaparin

Authors	No. of Pregnancies	Maternal VTE	Antenatal Bleeding Events	Postpartum Bleeding Events	Neonatal Events	Comments
Greer et al[42]	2777	1.37%	0.43%	0.94%	NR	1.8% allergic skin reactions; no HIT
Leperq et al[41]	624	1.3%	1.8% (9.8% nonserious)	1.4% (3.7% nonserious)	2.5% congenital anomalies; 1.1% serious neonatal hemorrhages*	
Ellison et al[43]	57	0%	1.7%*	7%	2%*	No HIT

HIT, heparin-induced thrombocytopenia; NR, not reported; and VTE, venous thromboembolism.

*Not attributable to LMWH

Importantly, the rate of postpartum hemorrhage (defined as a blood loss >500 mL after a vaginal delivery or >1000 mL after a cesarean delivery), is not significantly higher than the background rate of 1% to 5%.[44] The lack of increase in postpartum hemorrhage among pregnant women using enoxaparin is supported in other studies.[45] The theoretical potential for increased bleeding may be mitigated by strategic timing of doses relative to labor and delivery. The blood loss among women using LMWH may be reduced by stopping therapy 24 hours before the onset of labor or converting to UFH as described above.[46]

The use of neuraxial analgesia during labor and delivery poses a significant concern in the anticoagulated gravida. Spinal injection and epidural catheterization carry a risk of spinal hematoma.[47] In the event that an urgent delivery is required, the longer half-life of LMWH increases the risk that the patient may have to undergo general anesthesia. To minimize risk of intrapartum bleeding, the American College of Obstetrics and Gynecology recommends either converting from LMWH to UFH in the last month of pregnancy or stopping LMWH 24 hours before a planned delivery. Neuraxial anesthesia may be safely administered 10 to 12 hours after a last dose of prophylactic LMWH or 24 hours after a last therapeutic dose.[47,48] At our institution, we restart anticoagulation 6 to 12 hours after delivery depending on the risk of the patient and the mode of delivery. If a patient has had epidural anesthesia, we remove the epidural catheter before restarting anticoagulation.

Nonheparin Anticoagulants

Alternatives to heparin and LMWH include direct and indirect Xa inhibitors, direct thrombin inhibitors, and heparinoids. Although the literature is sparse with respect to the use of these agents in pregnancy, there may be a role for their use in women who have a history of heparin-induced thrombocytopenia, those who have a heparin allergy, or who would benefit from longer-acting anticoagulation.

Factor Xa Inhibitors

Heparin and LMWH affects factor Xa via its effects on antithrombin and factor II. Fondaparinux is an indirect factor Xa inhibitor with the largest collection of case-based data in pregnancy.[48–54] Two direct factor Xa inhibitors, argatroban and lepirudin, have published human data in pregnancy.[55–57] Fondaparinux is recommended by the American College of Obstetrics and Gynecology for anticoagulation in the setting of heparin-induced thrombocytopenia or other heparin allergy. In vitro studies do not demonstrate any passage across models of the human placenta.[58] However, a recent small study confirms earlier observations of neonatal anti–factor Xa levels at ≈10% of maternal levels.[45,59] This raises the possibility that fondaparinux may cross the human placenta in small doses. Prior studies on the safe and effective use of fondaparinux have used the same weight-based prophylactic and therapeutic doses used in the nonpregnant population. All available data describe subcutaneous administration only.

Retrospective and prospective cohort data show no difference in any major bleeding complications of the mother or newborn. Obstetric data are available comparing fondaparinux with enoxaparin for recurrent pregnancy loss.[48] The 29 pregnancies in which fondaparinux was used did not result in any birth defects or severe maternal or neonatal bleeding complications. Multiple case reports attest to the successful safe use of fondaparinux in pregnancy.[50–54] Its long half-life (15–17 hours) allows once daily subcutaneous dosing but also raises concerns for prolonged anticoagulant activity up to 48 hours after the last dose.[60] Transition to a shorter-acting agent before a planned cesarean delivery or vaginal delivery with neuraxial anesthesia would be necessary because fondaparinux cannot be reversed pharmacologically. In addition, because it is largely renally cleared, anti-Xa levels should be followed carefully in women with preeclampsia and women with renal insufficiency.

Data are emerging regarding the use of oral Xa inhibitors in pregnancy. Preclinical animal data suggest that rivaroxaban crosses the placenta and may have adverse fetal effects, and increasing maternal hemorrhage risk, as well.[61–63] The same animal data demonstrate that rivaroxaban is present in breast milk. Pregnant women were excluded from human clinical trials. There is 1 case report available of a woman whose history of 2 deep vein thromboses and pulmonary embolism was managed with continuous anticoagulation using rivaroxaban who was found to be pregnant at 19 weeks.[64] At that point, she was transitioned to enoxaparin. She had an unremarkable pregnancy and the neonate had a normal birthweight and essentially normal newborn period other than transitioning off of the mother's maintenance methadone. There are no published case reports about the use of apixaban or adoxaban and pregnancy. At this point, the expert consensus is that more data are needed before these medications can be used routinely in pregnancy.[65,66]

Direct Thrombin Inhibitors

There are several case reports of lepirudin use in the first and third trimester with interval transition to coumadin in some cases.[67–70] Lepirudin can be administered both intravenously and subcutaneously potentially expanding its outpatient utility.

Argatroban is a direct thrombin inhibitor. Animal studies by the manufacturer show no embryotoxicity of argatroban in rats or rabbits at low doses.[71] Doses used in animal studies were limited by the solubility of the medication, and thus do not offer strong evidence for safety in humans. Argatroban is administered via intravenous infusion only, limiting its outpatient use. However, its relatively short half-life of 39 to 51 minutes allows for a short time interval before neuraxial anesthesia.[72] Case reports suggest a role for argatroban use specifically during the induction of labor, given this short half-life. In contrast to the volume of literature showing no increased rate of postpartum hemorrhage above the national average for other anticoagulants, there may be an increased risk for postpartum hemorrhage with argatroban.[55–57] Thus, this medication should be used with caution and, like all anticoagulants with a long half-life, only in a setting with adequate blood bank support.

Dabigatran is a new oral antithrombin medication. Ex vivo studies of placental transfer demonstrate that dabigatran and, to a lesser extent, its prodrug, dabigatran etexilate mesylate, cross the human placenta.[73] Given the evidence for fetal exposure, dabigatran should not be used in pregnant women.

Table 4. Alternative Antiplatelet Therapy

Medication	FDA Class	Special Obstetric Considerations	Ability to Cross Placenta
Clopidogrel	B	No reported complications	Unlikely
Prasugrel[89]	C	No reported complications	Unknown
Ticlopidine[90]	D	Platelet inhibition in fetal cord blood	Yes
Eptifibitide[91]	C	Short half-life may allow safe use proximal to delivery	Unknown

FDA indicates Food and Drug Administration.

Medications: Antiplatelet Agents

Aspirin

Aspirin modulates platelet function via permanent acetylation of platelet cyclooxygenase. In animals, the use of high-dose aspirin, up to 20 mg/kg, in the third trimester can cause constriction and premature closure of the fetal ductus arteriosus.[74] For this reason, aspirin is a Food and Drug Administration category D drug. However, there is no evidence that low-dose (60–100 mg daily) aspirin has any effect on the ductus arteriosus.[75–77] Data analyzed from multiple large trials of various uses of aspirin during pregnancy strongly suggest that aspirin does not increase maternal or fetal bleeding risks, risk of placental abruption, or congenital anomalies.[78–81] Large studies examining the use of low-dose aspirin continued through delivery have not shown any increase in complications of neuraxial anesthesia.[82] Low-dose aspirin (75–100 mg) once daily is recommended by the AHA for pregnant patients with either a mechanical prosthesis or bioprosthesis in the second and third trimesters.[13] In our practice, we keep women on low-dose aspirin through the first trimester as well.

Clopidogrel

Clopidogrel inhibits platelet aggregation and activation by preventing binding of fibrinogen to the adenosine diphosphate receptor.[83] Animal studies in rats and rabbits have shown no adverse pregnancy effects in doses >65 times the human dose based on body surface area.[84] These studies have also identified the excretion of clopidogrel and its metabolites in milk of rats. No reports are available on the use of clopidogrel in human lactation. Based on limited animal data, clopidogrel is listed as category B by the Food and Drug Administration.

The primary obstetric risk with the use of clopidogrel is potential increased risk for intrapartum and postpartum hemorrhage. In nonpregnant patients, the use of clopidogrel within 7 days of surgery is associated with increased risk of significant bleeding.[85] There is no evidence that clopidogrel increases placental abruption or other antepartum obstetric bleeding events. Additionally, thus far, there are no reports of fetal hemorrhagic events or excessive neonatal bleeding.[86–88] In our practice, we hold clopidogrel 7 days before a scheduled delivery to minimize the risk of postpartum hemorrhage.

As with the anticoagulants, the administration of neuraxial anesthesia with clopidogrel raises the risk of spinal or epidural hematoma to an unacceptable level. Women who have used clopidogrel within 7 days should be counseled for alternative pain management during labor or general anesthesia for a cesarean delivery should they present in labor earlier than planned.

Overall, the paucity of data about antiplatelet agents beyond aspirin and clopidogrel precludes any evidence-based recommendations. Consideration may be given to stopping clopidogrel 7 days before a planned delivery. Transition to a glycoprotein IIb-IIa inhibitor, such as eptifibatide infusion (Table 4), is an option in women for whom antiplatelet therapy is essential.

Specific Clinical Considerations

Venous Thromboembolism

Risk of VTE is increased in pregnancy, particularly in the postpartum period. Pregnant women with risk factors for VTE or recurrent VTE should be risk stratified. The American College of Obstetrics and Gynecology offers concrete recommendations synthesized in part with the American College of Chest Physicians recommendations requiring anticoagulation in at-risk pregnant women (Table 5).

Women with low-risk thrombophilias such as factor V Leiden heterozygotes, prothrombin gene mutation heterozygotes, or - a protein C or S deficiency can be managed with a stepwise approach according to their medical history. Decisions regarding surveillance or prophylactic anticoagulation in the woman with no personal history of VTE should also incorporate family history of VTE. Women with affected first-degree relatives may be at higher risk. With each stratum of risk, the threshold to anticoagulate postpartum should be lower than antepartum, because this is the most thrombogenic period.

Women without thrombophilia are stratified differently. There is a dearth of data on the care of pregnant women with a history of VTE. Two small randomized, controlled trials assessing the safety of VTE prophylaxis in comparison with placebo or no treatment were both underpowered to show any difference in primary outcome.[92,93] Recommendations are therefore based on the likelihood of recurrence in the setting of the high-estrogen state of pregnancy. Women with unprovoked VTE or a history of ≥2 episodes of VTE are considered unacceptably high risk and should be anticoagulated regardless of context of the original events. See Table 2 for dosing recommendations.

If anticoagulation is needed for risk of VTE, our practice is to use LMWH as a first-line agent. We transition women to an equivalent dose of subcutaneous UFH at 36 weeks to minimize the risk of bleeding or anesthesia complications should spontaneous labor occur. In some select situations, we continue LMWH until 24 hours before a planned cesarean delivery or induction of labor. If a woman is therapeutically anticoagulated for acute VTE, we transition either to subcutaneous UFH dosed to reach target activated partial thromboplastin time or admit before delivery and transition to intravenous UFH infusion. Given the rarity of heparin-induced thrombocytopenia in pregnancy, platelet counts are not checked routinely when heparin therapy is initiated. We give women the option of continuing LMWH or transitioning to warfarin postpartum.

Mechanical Heart Valves

The management of mechanical heart valves in pregnancy poses a unique challenge. Although the newer bioprosthetic valves carry lower thrombosis risk, the superimposed

Table 5. Recommended Anticoagulation Strategies[32]

Indication	Antepartum	Postpartum (6–12 wk)
High-risk thrombophilia*		
No history of VTE	Prophylactic dosing	Prophylactic dosing
History of VTE	Consider intermediate or therapeutic dosing	Intermediate or therapeutic dosing
Low-risk thrombophilia†		
No history of VTE	Surveillance only or prophylactic dosing if additional risk factors	Surveillance only or prophylactic dosing if additional risk factors
History of VTE	Surveillance only or prophylactic dosing	Prophylactic dosing
History of single VTE		
In setting of pregnancy/estrogen	Prophylactic dosing	Prophylactic dosing
Other provoked	Surveillance	Surveillance
Unprovoked	Prophylactic dosing	Prophylactic dosing
Acute thromboembolism	Therapeutic dosing	Therapeutic dosing
History of 2+ VTE	Prophylactic or therapeutic dosing	Prophylactic or therapeutic dosing

VTE indicates venous thromboembolism.

Reproduced from Thromboembolism in pregnancy. ACOG Practice Bulletin 123. American College of Obstetricians and Gynecologists. *Obstet Gynecol.* 2011;118:718–729.[32]

*Antithrombin deficiency, compound heterozygote for prothrombin mutation and factor V Leiden, homozygote for prothrombin or Factor V Leiden.

†Factor V Leiden heterozygote, prothrombin gene mutation heterozygote, protein C or S.

hypercoagulability of pregnancy places these women at significantly elevated risk of a thromboembolic event. Women with mechanical heart valves have several choices for anticoagulation during pregnancy, but no option is without significant risks to the mother and fetus. The risk of thromboembolic events and valve thrombosis depends on the type and location (mitral > aortic) of the mechanical valve, and other factors, as well, including history of a previous thrombotic event, atrial fibrillation, or multiple prosthetic valves.

The 2014 AHA/ACC Valvular Heart Disease Guideline recommends dose-adjusted LMWH at least twice daily in the first trimester and warfarin in the second and third trimesters.[13] Use of UFH anticoagulation in a patient with a mechanical heart valve carries a 29% to 33% risk of life-threatening thrombosis with a 7% to 15% risk of mortality.[94] Sillesen reported a 30-year experience from Denmark in 79 women who had 155 pregnancies following valve replacement. Four women (5%) had thromboembolic events (all with mitral prostheses on UFH) and 2 women (2.5%) died, one of heart failure and one of postpartum bleeding.[95]

The use of LMWH during pregnancy for women with mechanical heart valves requires meticulous attention to dosing and frequent monitoring. Weight-based dosing is not appropriate for the pregnant patient with a mechanical heart valve.[96] Both the AHA/ACC and the European Society of Cardiology recommend a higher target anti-Xa level for pregnant patients, 0.8 U/mL to 1.2 U/mL 4 to 6 hours after dosing.[13,97] Serum levels will vary across gestation because of increased renal clearance and volume of distribution. Both the American College of Chest Physicians and the manufacturers of Lovenox cite a target peak anti-Xa of 1.0 U/mL 4 hours after subcutaneous administration. In 1 retrospective study of 31 women with mechanical heart valves undergoing 47 pregnancies, there was a ≈15% incidence of thrombotic complications, all associated with noncompliance or subtherapeutic anti-Xa levels.[98] James et al[99] managed pregnant women with mechanical heart valves with LMWH targeted at 1.0 U/mL 4 hours after administration and noted a 22% rate of thromboembolic events. Quinn et al[100] investigated the use of LMWH with a higher target anti-Xa level of 1.0 to 1.2 IU/mL among 11 pregnant women with mechanical heart valves. This required an average increase in the original weight-based LMWH dose of 54% with their increased target and surveillance protocol. One patient experienced a valve-related thrombosis, and there were 3 major bleeding complications.

Yinon et al[101] prospectively followed a cohort of 17 women (23 pregnancies) with mechanical left-sided heart valves receiving LMWH and low-dose aspirin. All women were managed by following anti-Xa levels 4 hours after dosing maintaining a target range of 1.0 to 1.2 U/mL. In this group of pregnancies, 22% (5) experienced adverse maternal cardiac events, 11% (3) experienced postpartum hemorrhage, and 4% (1) experienced a maternal thromboembolic event that resulted in fetal and maternal death. The occurrence of maternal death attributable to thromboembolism despite therapeutic levels of LMWH in this study highlights the limitation of LMWH safety among women with mechanical heart valves.

Chowdary et al[102] compared anti-Xa levels with parameters of thrombin generation assay in 41 pregnant women on LMWH and 40 pregnant controls. The thrombin generation assay directly measures the capacity of plasma to generate thrombin and has been used in previous studies to demonstrate interindividual variation in response to heparin and other anticoagulants.[103,104] They found a positive correlation between anti-Xa levels and the thrombin generation assay. However, using their methodology, they saw a high degree of interindividual variability of thrombin suppression in the pregnant cohort despite therapeutic anti-Xa levels. They propose that this finding may explain the data suggesting LMWH failure in high-risk pregnant women such as those with mechanical heart valves. There is not adequate data at this time to support the routine use of the thrombin generation assay.

Table 6. Recommended Regimens for Pregnant Patients With Mechanical Heart Valves

	Recommended Regimen	Class	Evidence Level
AHA/ACC, 2014[13]	• Warfarin in the second and third trimesters	I	C
	• Warfarin in the first trimester if dose <5 mg/d	IIa	B
	• Adjusted dose of LMWH or UFH in the first trimester if warfarin dose is >5 mg/d	IIa	B
	• Low-dose aspirin in addition with mechanical prosthesis or bioprosthesis	I	C
ESC, 2011[97]	• Warfarin in second and third trimesters	I	C
	• Warfarin in the first trimester if dose <5 mg/d	IIa	C
	• Warfarin in the first trimester if dose >5 mg/d	IIb	C
	• Adjusted dose of LMWH or UFH between weeks 6 and 12 with warfarin before and after	IIb	C
CHEST, 2008[94]	• Adjusted dose of LMWH throughout pregnancy	I	B
	• Adjusted dose of UFH throughout pregnancy	I	B
	• Adjusted dose of UFH or LMWH until week 13, then transition to warfarin	I	B
	• LDA in addition if high risk of thromboembolism	II	C

AHA/ACC indicates American Heart Association/American College of Cardiology; CHEST, American College of Chest Physicians; ESC, European Society of Cardiology; LMWH, low-molecular-weight heparin; and UFH, unfractionated heparin.

The recommendations from the European Society of Cardiology, AHA, and American College of Chest Physicians are summarized in Table 6. At our institution, we individualize care based on the type of valve, hemodynamics, and anticoagulation history. With LMWH use, once target antifactor Xa levels are achieved, we check levels on a weekly basis. For our highest-risk women, we advocate first-trimester LMWH followed by warfarin with return to either LMWH or hospital admission with heparin infusion (with an activated partial thromboplastin time >2 times control) for the last few weeks of pregnancy. We do not use SCH for pregnant patients with mechanical heart valves. We routinely induce labor at 37 to 38 weeks, halting heparin infusion only for placement of regional anesthesia and when delivery is anticipated in the next four hours. Cesarean delivery is reserved for those patients with an obstetric indication.

Antiphospholipid Syndrome

APLS is defined by clinical criteria – either poor obstetric history or vascular thrombosis – in the setting of specific laboratory abnormalities (see Table 7). The antiphospholipid antibodies include lupus anticoagulant, anticardiolipin antibody, and anti-β_2-glycoprotein.[105] Laboratory criteria for APLS is the presence of ≥1 of these antibodies at levels above the 99th percentile on 2 occasions at least 12 weeks apart. Women who are positive for all 3 of these antibodies carry a risk of a thrombotic event of 5.3% per year.[106] Antiphospholipid antibodies are challenging to assay, with false-positive rates as high as 25%.[107] Testing is ideally done when the patient is stable and should be repeated in 12 weeks to confirm results.[108] In our practice, we often perform antiphospholipid screening during pregnancy after taking a detailed obstetric history and initiate therapy based on results. We repeat testing postpartum after completion of anticoagulation therapy.

The association between circulating antiphospholipid antibodies and recurrent pregnancy loss is well established.[109,110] Women with obstetric manifestations of APLS benefit from the combination therapies of aspirin and heparin. Administration of low-dose aspirin alone can modulate risk of fetal loss.[111] Several meta-analyses have consolidated the data of multiple small trials assessing prophylactic UFH plus aspirin in comparison with aspirin alone and found the combination to be more effective. UFH with aspirin reduced spontaneous abortion and increased the live birth rate in comparison with aspirin alone.[112,113] Although the data on LMWH with or without aspirin are limited, extrapolation from the success of LMWH in other pregnancy applications suggests that it is an appropriate choice for treating the pregnant woman with APLS.

Women with a history of thrombosis and laboratory evidence of antiphospholipid antibodies should be anticoagulated according the same parameters described above for women with thrombophilia and a history of VTE (see Table 5). If the woman also meets obstetric criteria, she should take a low-dose aspirin in addition to using anticoagulation. The patient who only meets obstetric criteria should be treated either with low-dose aspirin or a combination of low-dose aspirin and prophylactic UFH or LMWH.

Preeclampsia and Intrauterine Growth Restriction

Preeclampsia is a disease specific to pregnancy that is defined by the presence of both maternal hypertension and proteinuria. It can affect multiple major maternal organs, and the placenta, as well, and consequently the fetus as manifested in IUGR.

Table 7. Antiphospholipid Clinical Criteria

Category	Clinical Criteria
Vascular thrombosis	One or more clinical episodes of arterial, venous, or small-vessel thrombosis, in any tissue or organ
Pregnancy morbidity	One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus
	One or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia or severe preeclampsia, or features consistent with placental insufficiency
	Three or more unexplained consecutive spontaneous pregnancy losses before the 10th week of pregnancy, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded

The pathophysiology of preeclampsia and IUGR is likely a continuum: both stem from abnormal placental implantation.[114] The early trophoblast invasion of the spiral arteries in the myometrium is inadequate and the placenta sustains ischemic injury, likely releasing stimulatory factors into maternal circulation.[115] Activation of platelets and the clotting cascade may predate clinical symptoms of preeclampsia.[116]

A series of small studies tested the hypothesis that, by inhibiting platelet cyclooxygenase activity and decreasing thromboxane, aspirin could prevent or treat preeclampsia.[117–119] These led to the Collaborative Low-Dose Aspirin Study in Pregnancy (CLASP) Trial. This large, randomized, placebo-controlled trial examined the ability of 60 mg of aspirin to prevent preeclampsia and IUGR in women at high risk of the disease and to treat preeclampsia and IUGR in women who already carried either diagnosis.[67] Treatment of the latter group was represented by safely extending the duration of the pregnancy. Nine thousand three hundred sixty-four high-risk women were randomly assigned to either 60 mg of aspirin daily or placebo. The observed 12% decrease in preeclampsia was not statistically significant. Furthermore, there was no statistically significant difference in birthweight, stillbirth, antepartum hemorrhage, placental abruption, or problems with epidural anesthesia. The aspirin group had a statistically significant 28% reduction in delivery before 37 weeks.

A meta-analysis of CLASP and the subsequent studies on women at moderate to high risk for preeclampsia found that prophylactic low-dose aspirin reduced the incidence of preeclampsia when initiated before 16 weeks.[120] This group also found that prophylactic low-dose aspirin started before 16 weeks reduced their secondary outcomes: severe preeclampsia, IUGR, gestational hypertension, and preterm birth.

Based on these data, it is our practice to treat women with a history of severe preeclampsia with a baby aspirin started at 10 to 16 weeks gestation and continued until 36 weeks gestation.

Conclusion

Pregnancy is a time of increased risk for thrombotic events. Knowledge of the balance of risks and benefits to mother and fetus support the safe use of anticoagulants and antiplatelet agents in pregnancy. In addition to maternal benefit in the setting of VTE and mechanical valves, these agents play an important role in preventing adverse obstetric outcomes such as preeclampsia, growth restriction, miscarriage, and abruption. Meticulous attention to dosage is essential because pregnant women increase their volume of distribution across trimesters. Timing of the use of anticoagulants by trimester and transition to short-acting agents in labor will decrease the risk of postpartum hemorrhage and other complications of labor and delivery. Given the elevated risk of maternal complications and preterm delivery, pregnant women with mechanical heart valves should be managed at tertiary care centers. Continued research is necessary to determine whether newer anticoagulants are safe in pregnancy; until then, aspirin, LMWH, UFH, and warfarin are the mainstay therapies for use in pregnant women.

Disclosures

None.

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